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Temporal Processing and Neurodevelopmental Disorders: Insights from Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and 22q11.2 Deletion Syndrome

Author

Brenner, Laurie Ashley

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Temporal Processing and Neurodevelopmental Disorders: Insights from Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and 22q11.2 Deletion Syndrome

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Laurie Ashley Brenner

2012

ABSTRACT OF THE DISSERTATION

Temporal Processing and Neurodevelopmental Disorders: Insights from Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and 22q11.2 Deletion Syndrome

by

Laurie Ashley Brenner
Doctor of Philosophy in Psychology
University of California, Los Angeles, 2012
Professor Steve Lee, Co-chair
Professor Carrie Bearden, Co-chair

The representation and utilization of temporal information is a basic human ability that permeates many aspects of daily life, such as estimating the duration of an event or predicting the duration of a behavioral response. The ability to discriminate temporal durations develops in infancy; however, the precision (i.e., consistency) of timing abilities improves from early childhood to adolescence. In recent years, there has been a surge of interest in the neurobiological basis of temporal processing, and the frontal-striatal systems have been implicated in second-range timing functions. Frontal-striatal abnormalities are well documented in attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and the genetic syndrome resulting from a deletion at 22q11.2 (22q11DS); therefore, temporal processing is a candidate endophenotype that may serve as a clinical indicator of aberrant

frontal-striatal function. The purpose of this study was to: (1) characterize time reproduction accuracy and variability in three different neurodevelopmental disorders, (2) model age-related changes in time reproduction accuracy and consistency, and (3) assess the relative contributions of symptom dimensions (inattention, hyperactivity, and autistic traits) to time reproduction performance. Data were collected over a three year period as an adjunct to ongoing research studies in ADHD, ASD, and 22q11DS. The time reproduction task was a previously validated measure of interval timing with target durations of 4, 8, 12, 16, and 20 seconds repeated four times each in random order. Time reproduction accuracy and consistency were analyzed separately in each of the three samples using repeated measures mixed effects regression. Across all samples, younger age was the most consistent predictor of time reproduction variability. High levels of inattention in the ADHD group were also associated with increased variability. Both the ASD and 22q11DS groups showed evidence of increased response variability relative to typically developing comparison groups; however, in the ASD group the effect of diagnosis was moderated by working memory. The results have implications for empirical investigations of temporal processing across multiple dimensions of psychopathology and highlight the importance of considering both response variability and developmental factors (e.g., maturation of frontal-striatal circuits) in the formation of new theories linking neurobiological substrates to the emergence of symptom constellations.

The dissertation of Laurie Ashley Brenner is approved.

Bruce Baker

Mirella Dapretto

Catherine Sugar

Steve Lee, Committee Co-chair

Carrie Bearden, Committee Co-chair

University of California, Los Angeles

2012

This dissertation is dedicated to

Professor Marian Sigman

(1941-2012)

Table of Contents

List of Tables and Figures

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Biographical Sketch

Laurie Ashley Brenner received her bachelor's degree in sociology and psychology from Wesleyan University in Middletown, Connecticut. She then crossed the country to research visual attention in autism at San Diego State University and was awarded a master's degree in psychology in 2006. Ms. Brenner entered the Clinical Psychology program at the University of California, Los Angeles (UCLA) in September of 2006. While at UCLA, Ms. Brenner minored in behavioral neuroscience, received a second master's degree, and satisfied the initial clinical requirements for a career in pediatric neuropsychology. She was also fortunate to have the mentorship of Professors Marian Sigman, Mirella Dapretto, Carrie Bearden, and Steve Lee. Ms. Brenner completed her pre-doctoral clinical internship in general neuropsychology at the Medical University of South Carolina in 2011. In September of 2012, she will begin a post-doctoral residency in pediatric neuropsychology at Children's Hospital Boston and the Department of Psychiatry at Harvard Medical School.

Chapter One

The precision of temporal reproductions is associated with age and inattention

Abstract

Objective: Although time reproduction is a plausible endophenotype for ADHD, much less is known about how symptom dimensions (inattention, hyperactivity/impulsivity) and chronological age affect time reproduction performance. We used a validated laboratory measure of time reproduction to assess the effects of DSM-IV symptom dimensions and chronological age on the accuracy and precision (i.e., consistency) of temporal reproductions, adjusting for working memory ability and general intelligence (IQ).

Method: Two-hundred and eighteen (218) ethnically diverse boys and girls (67% male) with (n=114) and without (n=104) DSM-IV ADHD between the ages of 6 and 9 (M=7.83, SD=1.17) were assessed on measures of time reproduction, IQ, and auditory working memory. The time reproduction task consisted of five interval durations (4, 8, 12, 16, and 20 seconds) presented four times each in random order.

Results: Repeated measures mixed effects regression analysis of age, inattention, and hyperactivity symptoms on time reproduction accuracy, adjusting for, sex, IQ, and interval duration, revealed a significant interaction between interval duration and inattention. Children with higher levels of inattention became increasingly inaccurate as interval duration increased. Using repeated measures mixed effects regression analysis to examine the effects of age, inattention and hyperactivity on time reproduction consistency, we observed significant main effects of inattention, age, and IQ as well as a significant interaction between inattention and interval duration; however, inclusion of ADHD symptom dimensions did not significantly improve model fit above and beyond age, IQ, interval duration, and sex, all of which had significant main effects on response consistency. The effect of auditory working memory was not significant in any of the models tested for either time reproduction accuracy or consistency.

Conclusion: These results suggest that the precision of temporal processing is associated with inattention and age. We highlight the importance of modeling both developmental factors and response variability in future studies of time reproduction.

Attention-deficit/hyperactivity disorder (ADHD) is characterized by an early-onset of developmentally inappropriate and impairing levels of inattention-disorganization and/or hyperactivity-impulsivity (American Psychiatric Association, 2000). Although ascertainment is based on the standards outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association [APA], 2000), DSM-IV criteria are inconsistently associated with underlying neurobiological processes and genetic factors (Robbins, Gillan, Smith, de Wit, & Ersche, 2011). Indeed, there is substantial heterogeneity in the clinical presentation of ADHD (e.g., comorbidity), likely reflecting multiple causal pathways across genetic, epigenetic, and environmental factors (see Taurines, Schmitt, Renner, Conner, Warnke, & Romanos, 2010 for a review). Reflecting this heterogeneity, the treatment utility of DSM-based designations are similarly inconsistent, leading experts to emphasize the value of functional behavior analysis and functional impairment in treatment planning relative to ADHD symptoms per se (Pelham, Fabiano, & Massetti, 2005). The limitations of diagnostic group membership (e.g., ADHD vs. control) have generated alternative approaches to integrate neurobiological markers with measureable behavior (Castellanos & Tannock, 2002; Robbins et al., 2011).

One such approach is the identification of endophenotypes, which are intermediate traits that conceptually and methodologically connect latent biological substrates of psychopathology with explicit phenotypes. Endophenotypes are continuous variables that are heritable, co-vary with the disorder, and co-segregate with family relatedness (Almasy & Blangero, 2001; Doyle, Willcutt, Seidman, Biederman, Chouinard, Silva, & Faraone, 2005; Gottesman & Gould, 2003). One promising endophenotype for ADHD is “sense of time,” or the ability to process temporal information and then to use that information to guide behavior. Temporal processing refers to

individual differences in the perception and estimation of the passage of time across a range of timescales (Buonomano, 2007). It is a potential endophenotype for ADHD because it has a plausible neurobiological substrate (Mauk & Buonomano, 2004), co-occurs with ADHD (Toplak, Dockstader, & Tannock, 2006), and shows evidence of heritability – e.g., children with ADHD are more impaired than controls on a measure of temporal processing ("time reproduction") and their unaffected siblings perform at a level intermediate to both groups (Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007). Time reproduction may be one of the more difficult temporal processing tasks for children because it requires both estimation of a temporal duration and execution of a corresponding motor response (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Zakay, 1990). Barkley et al. (1997) first associated time reproduction with ADHD, with subsequent studies suggesting poor accuracy and increased variability in ADHD probands, especially in the visual domain (Toplak et al., 2006; West, Douglas, Houghton, Lawrence, Whiting, & Glasgow, 2000). Although time reproduction has been associated with ADHD, the generalizability of previous results is limited by relatively small sample sizes (Bauermeister, Barkley, Martinez, Cumba, Ramirez, Reina, Matos, & Salas, 2005; Kerns, McInerney, & Wilde, 2001; McInerney & Kerns, 2003; Meaux & Chelonis, 2003; A. Smith, Taylor, Rogers, Newman, & Rubia, 2002; West et al., 2000), inclusion of only the combined subtype (Hurks & Hendriksen, 2011; Kerns et al., 2001; McInerney & Kerns, 2003), or treatment of all subtypes as a single ADHD group (Huang, Yang, Zou, Jing, Pen, McAlonan, & Chan, 2012).

One of the few studies of ADHD subtypes (i.e., Inattentive vs. Combined type) suggested that Combined type children were more variable in their reproductions than Inattentive type children (Mullins, Bellgrove, Gill, & Robertson, 2005); however results have been mixed, with

some evidence for no difference between ADHD subtypes (Bauermeister et al., 2005; West et al., 2000). The overall validity of ADHD subtypes has also been strongly questioned (Willcutt, Nigg, Pennington, Solanto, Rohde, Tannock, Loo, Carlson, McBurnett, & Lahey, 2012) and factor analytic studies support a single ADHD factor with separable sub-factors of inattention and hyperactivity (Toplak, Sorge, Flora, Chen, Banaschewski, Buitelaar, Ebstein, Eisenberg, Franke, Gill, Miranda, Oades, Roeyers, Rothenberger, Sergeant, Sonuga-Barke, Steinhausen, Thompson, Tannock, Asherson, & Faraone). Crucially, subtype comparisons (e.g., Combined type versus Predominantly Inattentive type) preclude investigation of the unique contributions of inattention and hyperactivity to time reproduction performance. Thus, the current literature on ADHD and time reproduction is limited because (1) it obscures characterization of meaningful within-group variability (i.e., within ADHD) and (2) the range of ADHD symptoms that we might expect to find in the general population is truncated by focusing only on children who exceed the diagnostic threshold. Preliminary results from dimensional models of inattention and hyperactivity with time reproduction are promising (e.g. Hurks & Hendriksen, 2011; Meaux & Chelonis, 2005). Meaux and Chelonis (2005) reported that hyperactivity was associated with time reproduction, although they did not examine inattention. Hurks and Hendriksen (2011) found that inattention, but not hyperactivity, was correlated with time reproduction, especially for the longer intervals (i.e., 45 and 60 seconds). Among the acknowledged limitations of this study were inclusion of only children with the combined type and extraction of ADHD symptoms from the Child Behavior Checklist rather than a diagnostic interview (Hurks & Hendriksen, 2011). Thus, there is a pressing need to further interrogate time reproduction in larger samples that differentially probe inattention versus hyperactivity using rigorous ascertainment of ADHD symptom dimensions with DSM-IV criteria.

A further consideration in studies of temporal processing is the importance of developmental perspectives, which are suggested by several lines of evidence. First, temporal processing is associated with the fronto-striatal-cerebellar system (Mauk & Buonomano, 2004; Meck, Penney, & Pouthas, 2008), which undergoes important maturational changes from childhood through adulthood (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). For example, during a time discrimination task, there were age-related increases in functional connectivity between inferior fronto-striatal and inferior parietal regions (A. B. Smith, Giampietro, Brammer, Halari, Simmons, & Rubia, 2011). Second, consistent with these neurodevelopmental changes, there are also age-related changes in the precision of temporal processing ability from early childhood to adolescence (Chelonis, Flake, Baldwin, Blake, & Paule, 2004; Pouthas, Droit, Jacquet, & Wearden, 1990). Importantly, even within a narrow age range (i.e., 5-9), there are age-related changes in the ability to discriminate shorter durations that emerge prior to the ability to discriminate longer durations (Zelanti & Droit-Volet, 2011).

Despite strong evidence that the ability to process time undergoes important maturational changes, the developmental course of temporal processing in ADHD is not well understood. Most studies controlled for age effects by matching the control and ADHD groups on age (e.g., see Huang et al., 2012; Kerns et al., 2001; Mullins et al., 2005), thus assuming developmental invariance of temporal processing. However, research suggests that time reproduction accuracy is more variable in younger children and that the gap between ADHD and typically developing children narrows considerably by age 11 (Rommelse et al., 2007). Cross-sectional studies comparing children to adults with ADHD have yielded mixed results with respect to age-related changes in time reproduction ability (Marx, Hubner, Herpertz, Berger, Reuter, Kircher, Herpertz-Dahlmann, & Konrad, 2010; Valko, Schneider, Doehnert, Muller, Brandeis, Steinhausen, &

Drechsler, 2010). Neither study found significant differences between children and adults with ADHD, suggesting that time reproduction deficits may persist into adulthood; however, these studies were limited by small sample sizes (less than 33 in each group) and treatment of age as a stratifying variable rather than as a continuous explanatory factor (Marx et al., 2010; Valko et al., 2010). Thus, the extent to which individual differences in time reproduction are attributable to developmental effects (i.e., delayed maturation of temporal processing abilities) and/or ADHD (i.e., inattention vs. hyperactivity) is largely unknown.

The association between age and temporal processing may reflect the developmental timeline of associated cognitive abilities, including IQ (Chelonis et al., 2004) and working memory (Zelanti & Droit-Volet, 2011). For example, in one study of typically developing children ages 5-9, digit span correlated with subsecond discrimination whereas a measure of auditory attention and response set was associated with durations longer than 15 seconds (Zelanti & Droit-Volet, 2011). The association between working memory and temporal processing is also supported by integrated neurobiological models of neuronal oscillations in the prefrontal cortex and the detection of cortical firing patterns by striatal neurons (Lustig, Matell, & Meck, 2005). There is therefore a theoretically plausible relationship between working memory and time reproduction at the neurobiological level that is consistent with task requirements (the sample interval duration must be "held" or maintained in memory during the reproduction); however, the association has not yet been clearly established in ADHD, as findings to date have been contradictory (e.g., Bauermeister et al., 2005; Kerns et al., 2001). The discrepant findings may reflect methodological differences (e.g., spatial versus auditory-verbal working memory); however, it is also conceivable that these studies, which were limited to relatively small samples, lacked sufficient power to detect an effect of working memory. To improve upon existing

research, we used a well-validated auditory working memory task to probe the relationship between working memory and temporal processing in a larger sample.

To review, it is unclear to what extent ADHD symptom dimensions are differentially associated with time reproduction performance. Given the biological plausibility that individual differences in temporal processing are sensitive to both developmental changes and ADHD, our goal was to assess the independent association of temporal processing with age, inattention, and hyperactivity in a large (n=218) and ethnically-diverse sample of six to nine year-old children with and without ADHD symptoms. Given that 40% of ADHD probands met criteria for oppositional defiant disorder (ODD), we included ODD symptoms to develop a more specific model on the association of ADHD and time reproduction. Based on previous findings, we hypothesized the following: (1) hyperactivity and inattention would each predict inaccuracy and inconsistency (i.e., variability) of temporal reproductions, and (2) accuracy and consistency would both increase with chronological age.

Methods

Participants

Participants were 218 ethnically diverse children (147 males, 71 females) between the ages of six and nine (M=7.83, SD=1.17). Participants were recruited through presentations to families attending self-help groups, educators, and advertisements mailed to local elementary schools, pediatric offices, and clinical service providers. Participants were excluded from the study if they had a Full Scale IQ (IQ) < 70, or if they had ever been diagnosed with a pervasive developmental disorder, seizure disorder, or any neurological disorder that prevented full participation in the study. Participants were required to live with at least one biological parent no less than half time and both parent and child were required to be fluent in English.

Procedures

Participant eligibility for the study was determined through an initial telephone screening. After eligibility was established, parents completed behavior rating scales and were invited to our research laboratory for in-person assessments of child behavior and family functioning. Approximately 15% of children were assessed in our laboratory with psychotropic medication (mostly stimulants). If a child normally received medication, his or her parents were instructed to provide ratings based on the child's un-medicated behavior. Similar procedures have been used in other ADHD studies, including the Multimodal Treatment Study of ADHD (Hinshaw, March, Abikoff, Arnold, Cantwell, Conners, & al., 1997; Lee, Lahey, Owens, & Hinshaw, 2008). All interviewers were blind to the child's diagnostic status, although the blind could not always be maintained over the course of the assessment. Children assented to all procedures. The Institutional Review Board approved all study procedures.

To improve the external validity of this study, participants with comorbid disorders were not excluded from participating. The most common comorbid conditions were oppositional/defiant disorder (ODD) and anxiety. Barkley and colleagues (2001) have shown that co-morbid ODD and parent ratings of anxiety/depression on the CBCL do not significantly impact time reproduction performance beyond the contribution of age, IQ, and ADHD severity; however, because ODD may be associated with assessment non-compliance, we included the number of ODD symptoms as an explanatory variable. The rationale for modeling the effect of ODD symptoms was to develop a more specific model of ADHD symptoms and time reproduction.

Parent Interview Measures

The *National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children, 4th edition* (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC-IV is a fully structured diagnostic parent interview of child psychopathology. Test-retest reliability for ADHD diagnoses from the DISC was between .51 and .64 in the DSM-IV Field Trials (Lahey, Applegate, McBurnett, Biederman, Greenhill, Hynd, Barkley, Newcorn, Jensen, Richters, & et al., 1994). We administered multiple modules, but focused on ADHD and ODD only. Specifically, we used the total number of inattention (range 0-9), hyperactivity (range 0-9), and ODD symptoms (range 0-8). The Cronbach alphas were 0.75, 0.60, and 0.74 for inattention, hyperactivity, and ODD, respectively.

Cognitive Measures

Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV; Wechsler, 2003). The WISC-IV is an individually administered intelligence test for children ages six to 16 that is considered to be a measure of general cognitive ability. Internal consistency for the WISC-IV FSIQ is 0.97 and test-retest reliability is between 0.89 and 0.93 (Williams, Weiss, & Rolfhus, 2003). We used three subtests (Arithmetic, Vocabulary, and Symbol Search) to estimate the full scale IQ (FSIQ). The composite of these three subtests correlated highly with the full 10 subtest estimate in the normative sample (r =.91; Sattler & Dumont, 2004). We also administered the Digit Span subtest, which has two components, Digit Span Forward and Digit Span Backward, that reflect separable constructs (rote auditory memory and attention versus manipulation of short term memory, respectively; Reynolds, 1997). We used the raw score from Digit Span Backward as a measure of auditory working memory, which is consistent with a prior study of time reproduction, working memory, and ADHD (Barkley et al., 2001).

Time Reproduction task (Barkley, 1998). This is a previously validated computerized task requiring estimation of a temporal duration and the execution of a motor response (i.e., the "reproduction") (Barkley et al., 2001). The task displays two light-bulbs simultaneously on the computer screen. The light-bulb on the left is turned on for an interval of 4, 8, 12, 16 or 20 seconds. When it goes off, the participant is asked to hold the space bar down to light up the bulb on the right for the same amount of time (i.e., to reproduce the interval). Participants practiced prior to the task to enhance comprehension. Each of the 5 temporal durations was repeated 4 times in random order, resulting in a total of 20 trials. No performance-based feedback was provided; however, given that motivational deficits associated with ADHD may influence performance (McInerney & Kerns, 2003), verbal praise was given to incentivize task engagement. Children also earned stickers for positive effort unrelated to task performance.

Data Analysis

The coefficient of accuracy (CoA) was used as the primary outcome measure of time reproduction performance. The CoA is calculated by dividing the subject's estimate of the temporal interval by the actual interval presented, yielding a percentage measure of error across the different durations. A score of 1.0 represents perfect accuracy whereas scores lower and higher than 1.0 represent under- and over-estimates, respectively. The CoA, which is also sometimes referred to as the duration judgment ratio, is a common outcome measures in studies of time reproduction (e.g., Hurks & Hendriksen, 2011; Kerns et al., 2001; Mullins et al., 2005; Plummer & Humphrey, 2008). Response *accuracy* was measured using the average CoA by averaging across the four repetitions of each trial type (4, 8, 12, 16, and 20 second durations). Response *consistency* ("variability") was measured by calculating the standard deviation of the four repetitions for each of the time durations. Variability has been less frequently examined than

accuracy, with most studies to dating have used the average of either the coefficient of accuracy or the absolute discrepancy; however, there is evidence to suggest that the standard deviation of the coefficient of accuracy, as a measure of intra-individual variability, is an important consideration in time reproduction studies (Plummer & Humphrey, 2008). The independent variables in our study were age (range 6-9), FSIQ, sex, auditory working memory (WISC-IV Digit Span Backward), interval duration (4, 8, 12, 16, or 20 seconds), as well as the number of inattention, hyperactivity, and ODD symptoms.

We constructed repeated measures linear mixed effects models to predict (1) response accuracy (average CoA) and (2) response consistency (standard deviation of CoA). The explanatory factors were modeled as fixed effects with a random intercept for each subject, allowing for individual variation in time reproduction capabilities. There were no *a priori* hypotheses about the pattern of correlations (or covariances) among repeated measures, so an unstructured covariance structure was specified. An alpha level of 0.05 was used for all statistical tests.

Results

Outliers and Correlations

Initial examination of the data revealed significant outliers that potentially biased mean estimates of performance. To be conservative, we only excluded outliers that were believed to reflect participant error (e.g., participant's finger slipped off the space bar). These outliers were defined as recorded values of 0.15 seconds and constituted 1.4% of the total number of observations. Treatment of outliers in the data, if they existed, has not been consistently reported on in the time reproduction literature; however, our approach is consistent with methods used by Marx et al. (2010) where 1.75 % of the data points were deemed to reflect participant error.

To examine multicollinearity, we computed pair-wise correlations among age, sex, IQ, auditory working memory (Digit Span Backward), and the number of inattention, hyperactivity, and ODD symptoms (Table 2). There was a strong correlation between hyperactivity and ODD (r=0.60), suggesting that included both may be redundant. To reduce noise in our model and to guard against the problems of multicollinearity (e.g., inflated standard error terms), we used a model comparison approach to determine whether hyperactivity or ODD would be the best fit for the data in combination with the other explanatory variables (sex, age, interval duration, IQ, and inattention).

Accuracy

We used a linear mixed effects models to examine the effects of interval duration, age, sex, IQ, auditory working memory, inattentive symptoms, and either hyperactivity or ODD symptoms on the *accuracy* of temporal reproductions. The dependent variable was the average coefficient of accuracy (across four trials) for each of the five interval durations. We fit a series of models removing non-significant variables at each step and successively adding the variables we hypothesized would be related to time reproduction accuracy. Age, sex, IQ, working memory, hyperactivity, and ODD symptoms were not significantly related to time reproduction accuracy. The optimal model was selected using the deviance test among models. Predicting time reproduction accuracy from inattention and interval duration, there was a significant interaction between inattention and interval duration, $F(4,864)=5.96$, $p<.0001$. The main effects of inattention, $F(1,864)=1.33$, $p=0.2487$, and interval duration, $F(4,864)=1.38$, $p=0.2373$) on response accuracy were not significant. Probing of the post-hoc interaction revealed that inattention was only significantly correlated with the four-second trials (r=0.17).

Consistency

The second set of analyses used linear mixed effects models to examine the association of age, sex, IQ, auditory working memory, inattention, and hyperactivity or ODD symptoms on response *consistency* (i.e., the standard deviation of the coefficient of accuracy for each of the five interval durations). To evaluate whether the number of inattention or hyperactivity symptoms would improve the prediction of response consistency, we fit a series of nested models to the data and then used the deviance test to compare the relative fit of each successive model. We ran the same series of models substituting ODD for hyperactivity symptoms. Overall, the models with hyperactivity performed better than those with ODD symptoms as a predictor of time reproduction consistency; thus, we retained hyperactivity instead of ODD. The association of auditory working memory was not significant in any of the models, and was excluded from the model.

Controlling for age, sex, IQ, interval duration, and inattention, the hyperactivity dimension was unrelated to time reproduction consistency. Using interval duration, inattention, IQ, age, and the interaction between interval duration and inattention to predict time reproduction consistency, there was a significant interaction between interval duration and inattention, $F(4,863)=3.99$, $p=0.003$. There were also significant main effects of IQ, $F(1,863)=7.59$, $p=0.006$, age, $F(1,863)=28.55$, $p<.0001$, and inattention, $F(1,863)=17.84$, $p<.0001$. The main effect of interval duration was not significant, $F(4,863)=0.34$, $p=0.8542$. Post-hoc contrasts to probe the significant interaction between inattention and interval duration using 20-second trials as the reference and adjusting for age and IQ indicated that higher levels of inattention were associated with greater variability only for the four-second interval. The deviance test for model comparison revealed that adding inattention and the interaction between interval duration and inattention did not significantly improve model fit above and beyond IQ,

age, sex, and interval duration. Therefore, the best model for the data was the more parsimonious model using only interval duration, age, sex, and IQ to predict time reproduction consistency. Excluding inattention from the model, there were significant main effects of interval duration, $F(4,867)=14.80$, $p<.0001$, IQ, $F(1,867)=15.38$, $p<.0001$, age, $F(1,867)=26.34$, $p<.0001$, and sex, $F(1,867)=4.52$, $p=0.0338$.

Discussion

Despite the fact that time reproduction shows promise as an endophenotype in ADHD, relatively few studies have examined the influence of ADHD symptom dimensions (i.e., hyperactivity and inattention) on both the accuracy and consistency of temporal reproductions. The main finding in this study was that the *consistency* of temporal reproductions varied significantly with age when we adjusted for IQ, sex, and interval length. More specifically, precision increased as a function of age. Age was unrelated, however, to *accuracy*. These results underscore the dissociation of precision (consistency) versus accuracy with respect to developmental change. This dissociation was further suggested given that precision, relative to accuracy, was far more associated with inattention, especially for longer interval durations. Crucially, previous studies of temporal reproduction used only two repetitions of each interval duration (e.g., Barkley et al., 2001; e.g., Bauermeister et al., 2005; Kerns et al., 2001), which may have masked the variability that was strongly featured in this study. The association of inattention with variability converges with previous evidence that response inconsistency is an important confound in studies of ADHD and cognitive function (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006), particularly for time reproduction paradigms (e.g., Barkley et al., 2001; e.g., Mullins et al., 2005). Our findings highlight the importance of modeling variability across multiple trials to explicitly test response consistency.

Our sample consisted of a relatively narrow developmental period (i.e., 6 to 9 years old); nonetheless, age was a significant predictor of time reproduction consistency. The association between age and time reproduction strongly suggests that a developmental approach to temporal processing that accounts for the maturation of cognitive processes is likely to provide additional traction on individual differences. Specifically, an approach based on matching according to chronological age may misrepresent patterns of association as attributable to clinical features of the disorder, whereas these differences may in fact be accounted for by developmental differences. For example, a comparison of children and adults with and without ADHD on measures of temporal processing suggested that differences in childhood may be more pronounced than they are in adulthood (Valko et al., 2010), which would be consistent with our findings.

From a neurofunctional perspective, our findings suggest that developmental differences in the fine tuning of time-sensitive networks may be contributing to behavioral deficits in temporal processing. The general neurofunctional network supporting temporal processing is believed to involve the cerebellum, basal ganglia and prefrontal cortex (Mauk & Buonomano, 2004). Conscious timing, such as duration estimation or reproduction of multi-second intervals, has previously been associated with working memory (Baudouin, Vanneste, Pouthas, & Isingrini, 2006) and the dorsolateral prefrontal cortex (Koch, Oliveri, Torriero, Salerno, Lo Gerfo, & Caltagirone, 2007), as well as dopaminergic connections within the basal ganglia (Hinton & Meck, 2004; Meck & Benson, 2002). In contrast, sub-second or millisecond timing has been associated with greater involvement of the cerebellum (Ivry & Spencer, 2004; Koch et al., 2007; Lewis & Miall, 2003). Other brain regions implicated in temporal processing include the frontal operculum, parietal cortex, posterior cingulate, (Lewis & Miall, 2003), anterior

cingulate, and supplementary motor area (Rubia, Halari, Christakou, & Taylor, 2009). Many of the same neuronal systems contributing to temporal processing in typically developing individuals have been implicated in children with ADHD, including abnormalities in the frontal-striatal-cerebellar circuit (Krain & Castellanos, 2006) such as volumetric reductions in the basal ganglia (Qiu, Crocetti, Adler, Mahone, Denckla, Miller, & Mostofsky, 2009), cerebellum (Berquin, Giedd, Jacobsen, Hamburger, Krain, Rapoport, & Castellanos, 1998) and frontal lobe (Valera, Faraone, Murray, & Seidman, 2007). To correlate behavioral measures of temporal processing in ADHD with brain function, future research would benefit from morphological studies of caudate volume as well as tractography using methods such as diffusion tensor imaging, or functional connectivity between regions of interest activated by a temporal processing paradigm. For example, future research could extend existing studies of fronto-striatal connectivity (e.g., A. B. Smith et al., 2011) to children and adolescents with ADHD in order to better understand developmental differences in frontal-striatal circuitry as a function of ADHD symptoms.

We hypothesized that hyperactivity would better predict inaccuracy and variability than inattention; however, this hypothesis was not confirmed. Parent ratings of inattention were more robustly related to time reproduction consistency and accuracy than hyperactivity or ODD symptoms. Children with elevated inattention showed increased variability across all interval durations, and the effect of inattention was especially pronounced for the four-second interval durations. This finding diverges from previous work that Combined type youth were more impaired than Inattentive type youth (Mullins et al., 2005) as well as research linking behavioral inhibition to time reproduction (Meaux & Chelonis, 2005). Interestingly, the association between inattention and time reproduction converges on one of the only studies to date that has

examined both the inattention and hyperactivity/impulsivity symptom dimensions (Hurks & Hendriksen, 2011). These findings also parallel evidence from the literature on temporal processing in typically developing children suggesting that the ability to process longer durations is related to the development of attentional resources (Zelanti & Droit-Volet, 2011).

In general, time reproduction *accuracy* was unrelated to age, sex, auditory working memory, IQ, or parent ratings of either hyperactivity or ODD symptoms. One possible interpretation of this finding is that by age six children have already developed a "sense of time," such that the basic ability to perceive and reproduce a temporal interval is intact and relatively robust in the aggregate to the influences of variable attention, restlessness, and impulsivity. This is suggested by habituation paradigms in very young infants (i.e., 6-10 months) which provide preliminary evidence that second-range duration discrimination is present early in development (Brannon, Suanda, & Libertus, 2007). It is also of potential relevance that the incentive system used during testing in our study (sticker chart, short breaks) was tailored to the motivational needs of the child, and this may have helped control for the effects of poor effort that are often associated with monotonous tasks such as time reproduction (McInerney & Kerns, 2003). The implication is that children with and without ADHD are capable of estimating time accurately, but performance often fluctuates as a function of both individual characteristics (e.g., inattention, age) and task demands (e.g., interval duration).

One possible limitation to the current study is the use of DSM-IV inattention and hyperactivity symptom counts. The symptom-based approach to ADHD has been criticized for yielding variables with skewed distributions (symptoms are classified as present/absent or present in varying degrees with restricted range) and for providing little guidance as to how significant discrepancies in parent- and teacher- reported symptoms should be reconciled

(Castellanos & Tannock, 2002). Moreover, as with every DSM disorder, each symptom is weighted equivalently, although individual symptoms may show stronger predictions of negative outcome or may be psychometrically superior in terms of discriminant validity (e.g., item response theory, Gomez, 2008). At present, there is no reliable alternative that would allow for a dimensional approach to ADHD while still permitting comparison to other studies of time reproduction in ADHD that have used DSM-IV symptom criteria.

Future studies should employ a similar model in different diagnostic groups to better understand the relationship between development, clinical features of ADHD, and temporal processing. In larger samples, particularly population-based ones, dimensional measures of inattention and hyperactivity may be more suitable than a categorical approach to answer questions about whether these symptoms are both necessary and sufficient for disrupted temporal processing. For example, high levels of inattention may be sufficient for decreased precision of temporal estimates, but not necessary in the sense that there are multiple pathways leading to increased variability (e.g., age or general cognitive ability). Moreover, temporal processing in other neurodevelopmental disorders, such as velo-cardio-facial syndrome (Debbané, Glaser, Gex-Fabry, & Eliez, 2005) and autism (e.g., Allman, DeLeon, & Wearden, 2011; Maister & Plaisted-Grant, 2011; Martin, Poirier, & Bowler, 2011; Szelag, Kowalska, Galkowski, & Poppel, 2004) may refine our understanding of whether disrupted temporal processing deficits are unique to ADHD or reflect a more general feature of aberrant neurodevelopment, possibly as a function of delayed maturation in frontal-striatal circuits.

This study suggests that age and inattention are strongly associated with response consistency whereas accuracy is not affected by age and only associated with inattention for four-second interval durations. Consistent with the crucial role of intra-individual variability as a

defining feature in ADHD (Castellanos et al., 2006), response inconsistency was a prominent characteristic of time reproduction performance in this study. The sensitivity of temporal processing tasks to response variability may lend critical traction in neuroimaging and genetic association studies as a potential biomarker of dopaminergic dysfunction and/or integrity of frontal-striatal pathways. Finally, this study has implications for temporal processing across other dimensions of psychopathology where the interplay of response variability and developmental factors (e.g., maturation of frontal-striatal circuits) are likely to be highly relevant for empirical investigations and also for the development of new theories linking biological substrates with the emergence of clinical symptoms.

Table 1. Demographic, IQ, and parent-report data

Group	**N**	**Age**	**Gender (m:f)**	**FSIQ**	**DSM-IV Inatt[3]**	**DSM-IV Hyper[4]**
Inattentive[1]	48	8.10(1.10)	32:16	100.56(14.68)	7.04(1.16)	2.39(1.61)
Hyperactive[1]	11	6.99(1.04)	9:2	111.45(13.41)	3.54(1.92)	7.45(1.03)
Combined[1]	55	7.67(1.16)	41:14	104.56(13.43)	7.55(1.17)	7.40(1.33)
Borderline[2]	13	7.84(0.81)	7:6	106.67(16)	4.31(1.18)	3.23(2.17)
Control	91	7.90(1.23	58:33	109.10(15.10)	1.52(1.63)	0.98(1.29)
Total	**218**	**7.83(1.17)**	**147:71**	**106.52(14.72)**	**4.55(3.12)**	**3.38(3.086)**

1. *Defined strictly by parent-reported symptom counts on the Diagnostic Interview Scale for Children (DISC)*
2. *DSM-IV Symptom Count = 5 in either or both categories*
3. *DISC Inattentiveness DSM-IV Symptom Counts (9 possible), Mean(SD)*
4. *DISC Hyperactivity DSM-IV Symptom Counts (9 possible), Mean(SD)*

Table 2. Correlation matrix

	Inattention	Hyperactivity	Digit Span Backward	IQ	ODD	Age
Inattention	1.0000					
Hyperactivity	0.5873*	1.0000				
Digit Span Backward	-0.1143	-0.1786*	1.0000			
IQ	-0.2351*	-0.0363	0.3571*	1.0000		
ODD	0.4218*	0.5989*	-0.0720	0.0022	1.0000	
Age	0.0331	-0.1680*	0.2886*	-0.0871	-0.0107	1.0000

*p<.05

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Chapter Two

A time to remember: working memory is associated with time reproduction in children with high-functioning autism

Abstract

Objective: Temporal processing has historically been associated with attention-deficit/hyperactivity disorder (ADHD). Recent evidence suggests that temporal processing deficits may also be a phenotypic characteristic of autism spectrum disorder (ASD); however, little is known about the effect of co-morbid attention problems on temporal processing in children with ASD. The purpose of this study was to assess the effects of ADHD symptomotology, working memory, and age on time reproduction in children with ASD and their typically developing peers.

Method: Twenty-seven individuals with ASD (ages 9-17) were compared to 25 age- and gender- matched typically developing individuals on measures of time reproduction, auditory working memory, and parent-rated ADHD symptoms. The time reproduction task consisted of five interval durations (4, 8, 12, 16 and 20 seconds) repeated four times each in random order. Repeated measures mixed effect regressions were run to predict time reproduction accuracy and consistency from group, interval duration, age, working memory, and ADHD symptoms.

Results: While children with ASD and their matched controls reproduced temporal intervals at a similar level of accuracy, significant between-group differences were observed in the consistency (i.e., variability) of their responses. Furthermore, the effect of diagnosis on consistency was moderated by working memory. Younger age and lower auditory working memory scores were each associated with reduced accuracy and increased variability. Co-morbid ADHD symptoms were not related to either accuracy or consistency.

Conclusions: These results argue against a pure timing deficit in ASD and suggest that response variability, age, and working memory are important considerations in future studies of temporal processing in ASD.

Autism is a neurodevelopmental disorder, or group of related disorders, characterized by impairment in three domains: social interaction, communication, and behavioral flexibility (DSM-IV, American Psychiatric Association, 2000). More recently, the term "autism spectrum disorder" (ASD) has been adopted to reflect the broader spectrum and dimensionality of autism phenomenology and etiology. Conceptualizing autism as a spectrum disorder (the "autisms") also draws attention to phenotypic heterogeneity (Geschwind & Levitt, 2007) and the need to identify intermediate traits more closely related to specific genetic etiologies (Levitt & Campbell, 2009) and brain function (Levy & Ebstein, 2009). To be useful, it is argued that these intermediate traits need not be bound to syndromic groups, but rather characterize dimensions at the behavioral level that are indicators of underlying neurofunctional integrity (Levy & Ebstein, 2009). In other words, moving away from the highly heterogeneous symptom clusters (e.g., social function, communication), it will be important to identify more homogeneous traits that can be quantified dimensionally, have a plausible neurobiological substrate, and could theoretically serve as clinical correlates of aberrant brain function.

Temporal processing, or sense of time, is one such intermediate trait that has a rich history in the neurosciences. Temporal processing refers to the basic human ability to "sense" or register the passage of time, connect that information to current behavior, and file it away for future use. Fueled by anecdotal and early empirical evidence that this basic ability may operate differently in ASD (Boucher, Pons, Lind, & Williams, 2007; Szelag, Kowalska, Galkowski, & Poppel, 2004; Wimpory, Nicholas, & Nash, 2002), the study of temporal processing and autism has gained momentum in recent years. Although temporal processing is a relatively novel area of ASD research, it is bolstered by a substantial literature on the measurement of time-related processes (e.g., time estimation, perception, production, and reproduction) and their associated

neurobiological substrates in typically developing individuals (e.g., see Mauk & Buonomano, 2004; Meck & Benson, 2002). The circuit believed to support millisecond- and second- range timing functions includes projections to and from the basal ganglia and frontal lobe as well as connections with the cerebellum (Mauk & Buonomano, 2004). It is therefore noteworthy that a thorough review and meta-analysis of published neuroanatomical studies of ASD reported increased total volume of the cerebral hemispheres, cerebellum, and caudate nucleus accompanied by a reduction in the size of the corpus callosum as the most consistent findings to date (Stanfield, McIntosh, Spencer, Philip, Gaur, & Lawrie, 2008). From a neurodevelopmental perspective, temporal processing therefore shows promise as a possible clinical correlate of cerebellar-striatal-frontal circuitry.

The developing literature on temporal processing in ASD has yielded mixed results thus far (e.g., see Gowen & Miall, 2005; Radonovich & Mostofsky, 2004; Wallace & Happe, 2008), although the preponderance of evidence supports aberrant second-range temporal processing (Allman, DeLeon, & Wearden, 2011; Maister & Plaisted-Grant, 2011; Martin, Poirier, & Bowler, 2011; Szelag et al., 2004). Cross-study comparison is complicated by differences in modality, interval duration, age range, and task structure. Several studies have reported results in relatively small samples (Allman et al., 2011; Szelag et al., 2004) which may be problematic in light of phenotypic heterogeneity in ASDs (Matson & Nebel-Schwalm, 2007; Matson & Shoemaker, 2009; Starr, Szatmari, Bryson, & Zwaigenbaum, 2003). The most commonly used paradigm has been temporal reproduction (Maister & Plaisted-Grant, 2011; Martin et al., 2011; Wallace & Happe, 2008) which requires participants to first attend to an auditory or visual stimulus that persists for a pre-specified duration and to then reproduce the perceived duration. There is evidence that adults with ASD are more variable and less accurate when asked to

reproduce durations ranging from 1-4 seconds presented in the auditory domain (Martin et al., 2011). In contrast, Wallace & Happe (2008) found that younger participants (9-18 years) with ASD did not differ from typically developing individuals when asked to reproduce auditory durations ranging from 2 to 45 seconds. In fact, time reproduction scores for shorter durations were slightly better in the ASD group relative to the control group when the authors accounted for outliers in the data (Wallace & Happe, 2008). More recently, in the visual domain, children with ASD (8-13 years) were shown to have reduced accuracy for short durations (<2 seconds) and long durations (45 seconds) but not for durations in the 4-30 second range (Maister & Plaisted-Grant, 2011). The children with ASD were also more variable when reproducing the shorter durations; however, it is difficult to draw conclusions about variability given that the estimate was based on two data points per duration (Maister & Plaisted-Grant, 2011). In spite of these limitations, the existing literature suggests that variability in temporal reproductions is likely to be an important consideration (Maister & Plaisted-Grant, 2011; Martin et al., 2011; Szelag et al., 2004). Adequate assessment of variability will require larger sample sizes as well as multiple repetitions of the same duration in order to calculate reliable estimates of error variance.

It is also worth mentioning that temporal processing deficits have been repeatedly demonstrated in ADHD (Toplak, Dockstader, & Tannock, 2006) and have been linked to variability in executive functions such as working memory (Bauermeister, Barkley, Martinez, Cumba, Ramirez, Reina, Matos, & Salas, 2005). There is preliminary evidence that memory may play a role in ASD as well; for example, temporal processing deficits were found to be associated with short-term visual-spatial memory (Maister & Plaisted-Grant, 2011) and auditory working memory (Allman et al., 2011); however, as with prior studies, the authors did not report

on the presence or level of co-morbid attention problems. Under the current diagnostic classifications system (DSM-IV, American Psychiatric Association, 2000), attention-related problems are subsumed by the ASD diagnosis even when children display clinically significant symptoms of ADHD. Estimates of ADHD symptoms in ASD are quite high (Leyfer, Folstein, Bacalman, Davis, Dinh, Morgan, Tager-Flusberg, & Lainhart, 2006), and have been shown to exacerbate deficits in verbal working memory (Yerys, Wallace, Sokoloff, Shook, James, & Kenworthy, 2009), raising the possibility that disrupted temporal processing is symptomatic of attention-related deficits rather than autism per se. Thus, in order to establish that temporal processing deficits are also characteristic of ASDs, quantification of co-morbid attention-related problems is imperative.

To address limitations in the literature to date, the aim of this study was to characterize the relative contributions of working memory and attention to time reproduction accuracy and consistency ("variability") in a sample of children with ASD, adjusting for differences in age and general intellectual ability (i.e., IQ). We hypothesized that duration reproductions would be more accurate and consistent in the control group relative to the ASD group. We also expected auditory working memory to be positively associated with response consistency and accuracy. With respect to attention, we predicted that consistency and accuracy of temporal reproductions would be inversely related to parent-ratings of ADHD symptomotology.

Methods

Participants

Twenty-seven (27) children and adolescents with a diagnosis of Autistic Disorder and 25 age- and gender- matched typically developing individuals ranging in age from 9 to 17 took part in the experiment. Demographic data are listed in Table 1. To determined eligibility, all

participants in the ASD group were seen at the UCLA Autism Evaluation Clinic for assessment of intellectual functioning and a diagnostic evaluation. All participants were determined to have developed language and to have a verbal IQ greater than 60. Exclusion criteria include history of head injury, seizures, other neurological disorders, and psychiatric disorders other than autism. Participants obtained a brain scan as part of the larger study under which these data were collected; therefore, additional exclusion criteria were a fear of enclosed spaces (claustrophobia) and any implanted metal.

Procedures

Participants were recruited through a combination of word-of-mouth (e.g., families who had participated recommend the study to friends or acquaintances) and referrals from pediatric offices, local schools, and other autism researchers at UCLA. Additional recruitment occurred through flyers posted on autism-related websites (e.g. www.autism.ucla.edu) and distributed at local events. Finally, some participants from previous brain imaging studies at UCLA checked a box on the consent form indicating their wish to be contacted for participation in future studies. All participants and their caregivers underwent the informed consent process as part of an ongoing study of brain structure and function in children and adolescents with ASD. The time reproduction data were collected over a one-year period (September 2009 to September 2010) at the Abramson-Lovelace Brain Mapping Center (ALBMC) at the University of California, Los Angeles (UCLA). The time reproduction task was an addition to an extensive battery of questionnaires, computerized measures, and brain imaging that participants completed over multiple days.

The autism evaluation included the *Autism Diagnostic Observation Schedule (ADOS)*, *Autism Diagnostic Interview Schedule – Revised (ADI)*, and behavioral observation by a clinician

specializing in autism spectrum disorders. The ADOS is a semi-structured interactive assessment completed directly with the child in 30-60 minutes (Lord, Rutter, DiLavore, & Risi, 2003). All children in the study had fluent speech and were therefore able to complete Module 3. The ADOS has been shown to have good inter-rater and test-retest reliability, and excellent specificity for autism versus non-spectrum (94%) and pervasive developmental disorder – not otherwise specified (PDD-NOS) versus non-spectrum (88%), but somewhat lower specificity for PDD-NOS versus autism (Lord, Risi, Lambrecht, Cook, Leventhal, DiLavore, Pickles, & Rutter, 2000). The ADI-R was used to assess developmental milestones and behavioral abnormalities that may be associated with any type of developmental delay, and which is of particular importance in the diagnosis of Autistic Disorder.

The parent-report version of the *Achenbach Child Behavior Checklist (CBCL)* consists of 118 questions that cover eight different behavioral domains. The Attention Problems subscale includes items related to inattention, distractibility, sustained attention, restlessness, and impulsivity. For the purpose of this study, it was used as a global measure of ADHD-related symptomotology. All raw scores for the Attention Problems subscale were converted to standard scores (T-scores; M=50, SD=10) using the Assessment Data Manager (ADM) software program.

The *Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV)* was used to assess general intellectual ability. In addition to the Full Scale Intelligence Quotient (FSIQ), the WISC-IV yields subtest scores in several domains, one of which is working memory. The Letter-Number Sequencing subtest was used as a measure of auditory attention and working memory. All raw scores were converted to standard scores (WISC-IV Scaled Score; M=10, SD=3).

Time Reproduction (TR) measures the individual's ability to estimate a temporal duration and to then utilize the estimate to execute a motor response, the "reproduction" (Barkley,

Edwards, Laneri, Fletcher, & Metevia, 2001). We used a previously-validated computerized time reproduction paradigm (Barkley, 1998b) that displays two light-bulbs simultaneously on the computer screen. The light-bulb on the left was turned on for an interval of 4, 8, 12, 16 or 20 seconds and when it went off the participant held the space bar down in order to "light up" the bulb on the right for the same amount of time (i.e., reproduce the interval). Prior to beginning the task, participants were given an opportunity to practice to ensure comprehension of task instructions. Each of the 5 temporal durations was repeated 4 times in random order, resulting in a total of 20 test trials. No performance-based feedback was provided; however, verbal praise and encouragement for effort were given to keep participants oriented and to maximize motivation to do well.

Data Analysis

The coefficient of accuracy (CoA) was used as the primary outcome measure of time reproduction performance. The CoA is calculated by dividing the subject's estimate of the temporal interval by the actual interval presented, yielding a percentage measure of error across the different durations. A score of 1.0 represents perfect accuracy whereas scores lower and higher than 1.0 represent under- and over-estimates, respectively. The CoA, which is also sometimes referred to as the duration judgment ratio, is a common outcome measures in studies of time reproduction (e.g., Hurks & Hendriksen, 2011; Kerns et al., 2001; Mullins et al., 2005; Plummer & Humphrey, 2008). Response *accuracy* was measured using the average CoA by averaging across the four repetitions of each trial type (4, 8, 12, 16, and 20 second durations). Response *consistency* ("variability") was measured by calculating the standard deviation of the four repetitions for each of the time durations. Variability has been less frequently examined than accuracy, with most studies to dating have used the average of either the coefficient of accuracy

or the absolute discrepancy; however, there is evidence to suggest that the standard deviation of the coefficient of accuracy, as a measure of intra-individual variability, is an important consideration in time reproduction studies (Plummer & Humphrey, 2008). The independent variables in our study were age (range 9-17), IQ, sex, interval duration (4, 8, 12, 16, or 20 seconds), and CBCL Attention Problems.

We constructed repeated measures linear mixed effects models to predict (1) response accuracy (average CoA) and (2) response consistency (standard deviation of CoA). The explanatory factors were modeled as fixed effects with a random intercept for each subject, allowing for individual variation in time reproduction capabilities. There were no *a priori* hypotheses about the pattern of correlations (or covariances) among repeated measures, so an unstructured covariance structure was specified. An alpha level of 0.05 was used for all statistical tests.

Results

Outliers and Group Differences

Initial examination of the data revealed significant outliers that biased mean estimates of performance. Taking a cautious approach, we only excluded outliers that were believed to reflect participant error (e.g., participant's finger slipped off the space bar). These outliers were defined as subject duration estimates of less than 0.15 seconds and amounted to 1.23% of the total number of observations.

Mean age, IQ, and gender distribution are listed in Table 1. There were no significant group differences for age, IQ, sex, or WISC-IV Letter-Number Sequencing task (auditory working memory). However, there was a statistically significant between-group difference for the CBCL Attention Problems subscale, $t(43)= 5.8858$, $p<0.0001$, with the ASD group

evidencing more problems than the control group. As expected, the distribution of attention problems within the control group centered on the normative mean with very little variability (M=51.53, SD=2.52). This was in contrast to the ASD group, for which parent ratings of attention problems were significantly higher than the normative mean and more widely distributed than in the control group (M=64.38, SD=9.25).

Accuracy

Repeated measures mixed effects linear regression analyses were run to predict accuracy of temporal reproductions from diagnosis (autism versus control), interval duration, working memory, and attention problems. Covariates included IQ, age, and sex. The factors IQ and sex were non-significant and were removed from further analysis. Thus, predictors in the final model were trial type, attention problems, auditory working memory, age, and the interactions auditory working memory by diagnosis, and auditory working memory by age. There was a significant interaction between working memory and age, $F(1, 204) = 4.28$, $p = 0.0399$ for time reproduction accuracy, with younger age predicting a greater reduction in accuracy for children who also had low working memory scores. There were significant main effects of both age, $F(1, 204) = 5.26$, $p = 0.0229$, and working memory, $F(1, 204) = 6.14$, $p = 0.0140$ on time reproduction accuracy. Diagnosis (i.e., ASD versus control), $F(1,204) = 0.96$, $p = 0.3289$, attention problems, $F(1, 204) = 0.24$, $p = 0.6247$, and trial type, $F(4, 204) = 1.24$, $p = 0.2937$, were not significant predictors of time reproduction accuracy.

Consistency

Repeated measures mixed effect linear regression analyses were run to predict consistency in temporal reproductions from diagnosis (autism versus control), interval duration, attention problems, and working memory. Covariates included IQ, age, and sex. The factors IQ

and sex were non-significant and were removed from the model. The final model included trial type, attention problems, auditory working memory, age, and the interactions auditory working memory by diagnosis, and auditory working memory by age. There were significant interactions between working memory and diagnosis, $F(1, 204) = 8.23$, $p = 0.0046$, and between working memory and age, $F(1, 204) = 17.45$, $p < .0001$ for time reproduction consistency. There were also significant main effects of age $F(1, 204) = 26.61$, $p < .0001$, working memory $F(1, 204) = 24.18$, $p < .0001$, and diagnosis $F(1, 204) = 8.70$, $p = 0.0036$ on time reproduction consistency. Attention problems, $F(1, 204) = 0.27$, $p = 0.6012$, and interval duration, $F(1, 204) = 1.16$, $p = 0.3288$, were not significant predictors of temporal reproduction consistency.

Following up on the significant between group differences in consistency, we replicated the analysis in the ASD group only to assess whether the effects of age and working memory on response consistency would remain significant, and whether we would also observe a within-group effect of attention problems. The rationale for this follow-up analysis was that attention problems and working memory were not equally distributed across groups (i.e., the range of values was restricted in the control group), potentially leading to spurious conclusions about the effect of working memory and attention problems on time reproduction. Repeated measures linear regression analyses were run within the ASD group to predict consistency in temporal reproductions from interval duration, attention problems, working memory, age and the interaction between auditory working memory and age. We observed significant main effects of age $F(1, 204) = 35.88$, $p < .0001$ and working memory $F(1, 204) = 34.18$, $p < .0001$ on response consistency, as well as a significant interaction between working memory and age, $F(1, 204) = 24.96$, $p < .0001$. Consistent with the between-group analysis, younger age predicted increased variability for children who also had lower auditory working memory scores. Attention problems

were not a significant predictor of temporal reproduction consistency within the ASD group, $F(1, 204) = 1.19$, $p = 0.2764$. These results corroborate the initial between-group analysis with response consistency as the dependent variable.

Discussion

The purpose of this study was to evaluate the effects of age, auditory working memory, ADHD symptoms, and ASD diagnosis on time reproduction *accuracy* and *consistency*. The primary hypothesis of this study was partially confirmed: children with ASD were *more variable* (less consistent) in their temporal reproductions than typically developing children. We also found that the effect of diagnosis on variability was moderated by auditory working memory ability. In other words, the difference in response consistency between children with ASD and typically developing children was more pronounced when auditory working memory scores were poorer. In support of evidence that the precision of temporal estimates is influenced by developmental changes (Chelonis, Flake, Baldwin, Blake, & Paule, 2004) we found that younger children were more variable, and this effect was moderated by auditory working memory ability. A follow-up analysis within the ASD group yielded identical results. Among children and adolescents with ASD, the ability to consistently reproduce temporal intervals is influenced by the interaction between chronological age and proficiency in maintaining and manipulating information in short term memory. Increased variability is consistent with a prior study of time reproduction in ASD (Maister & Plaisted-Grant, 2011) and our results show that this effect persists when the number of repetitions per interval duration is increased.

These results also provide evidence that the ability to *accurately* reproduce a temporal duration is influenced by both age and working memory, but not by ASD diagnosis. Children with ASD were just as accurate in their temporal reproductions as the typically developing

children. In the sample overall, younger age and lower auditory working memory scores were associated with reduced accuracy, with errors tending to be in the direction of underestimations.

The secondary hypothesis of this study, that variability in time reproduction performance would be positively correlated with parent-ratings of ADHD symptomotology, was not confirmed. Similarly, higher parent-ratings of attention problems did not predict reduced accuracy. Thus, although children with ASD tended to have more attention-related problems than typically developing children in our sample, these difficulties were not predictive of reduced accuracy or greater variability for time reproduction. Concluding that co-morbid attention problems in ASD are not related to time reproduction performance might be premature in light of several limitations to this study that should be addressed in future studies of temporal processing in ASDs. First of all, subjects were recruited for participation in an fMRI study and this may have screened out any children whose parents were concerned about their ability to stay still for extended periods of time. In other words, it is possible that this sample had much lower rates of attention-related problems than would be expected to occur in a more representative sample of high functioning children with autism. A second limitation to this study was the use of the CBCL Attention Problems subscale in place of formal diagnostic criteria for ADHD (e.g., DSM-IV symptom counts from a structured parent interview). This could be addressed in future studies by administering a DSM-IV-based ADHD checklist or the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children, 4th edition (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000).

This study fits with a growing body of literature implicating temporal processing deficits in ASD (Allman et al., 2011; Maister & Plaisted-Grant, 2011; Martin et al., 2011; Szelag et al., 2004); however, more research is needed to untangle the precise nature of the deficit, its

relationship to other cognitive and behavioral processes, and the degree to which it characterizes the majority of individuals with ASD, as opposed to only a subset. One of the many questions arising from this line of research is whether temporal processing can be linked to functional deficits in brain development, possibly in cerebellar-striatal-frontal circuitry. To answer this question, future research could use brain morphology (e.g., caudate volume) or connectivity between the basal ganglia and frontal regions to assess correlations with time reproduction performance. It is also possible that temporal processing deficits reflect a more general underlying vulnerability in neurobiological systems that are also important for attention regulation and working memory, which would fit with integrative theoretical models of oscillatory neuronal firing in frontal-striatal circuits (Lustig, Matell, & Meck, 2005). Inclusion of attention and working memory measures will help clarify how these related systems are supported by overlapping or distinct neurofunctional systems in neurodevelopmental disorders.

From a broader theoretical perspective, deficits in temporal processing could have a highly dispersed impact on other cognitive processes (e.g., language) and social behavior (Boucher et al., 2007; Wimpory et al., 2002); however, there is very little data at present to support this assertion. In one study of temporal processing in children with high-functioning autism, Boucher and colleagues (2007) demonstrated that children with autism fail to show a developmentally appropriate tendency to think 'backwards' and 'forwards' across time, are impaired in their ability to represent qualitative change across time, and struggle to conceptualize successive temporal events as a unitary whole. Initial findings were replicated in a second group of children and adolescents with ASD, with a series of control tasks employed to rule out the possibility that initial findings were attributable to other task demands (e.g., ability to draw inferences, generate varied responses, understand or have experience with task-specific events)

rather than temporal processing per se (Boucher et al., 2007). These results suggest that there are functional implications of an impaired sense of time that are evident in how children with autism perceive chronological sequences and use past and future events to contextual the present. There is also preliminary evidence from a study by Allman and colleagues (2011) that laboratory measures of temporal processing have ecological validity in predicting parent-ratings of their child's sense of time, as measured by the "*It's About Time"* questionnaire (Barkley, 1998a).

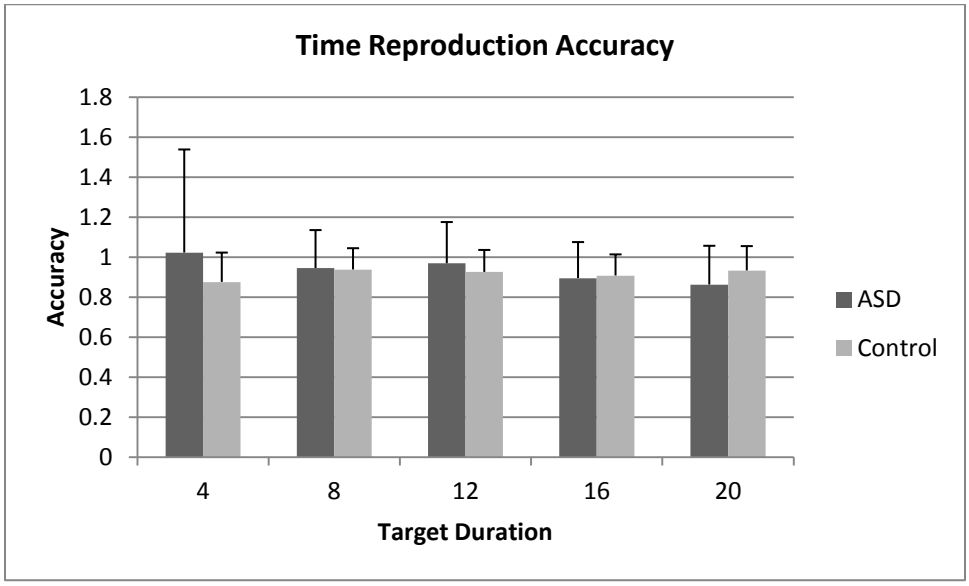
Time is an elemental feature of subjective experience that is potentially relevant to a wide range of activities necessary for daily living. To establish deficits in temporal processing as a useful phenotypic marker in ASD will require additional evidence documenting associated functional impairment. Possible avenues of inquiry might include assessment of temporal processing as it relates to general adaptive function, social skills, language development, or academic function. A better understanding of how deficits in temporal processing may impact daily living skills has the potential to revise our approach to behavioral intervention in ASD. For example, environmental contingencies are time-sensitive and may be influenced by a poor perception of elapsed time. Simple temporal adjustments in the delivery of rewards or consequences for certain behaviors could have implications for treatment effectiveness. Visual aids to help mark the passage of time and keep track of temporal order may also be helpful for children who have a known difficulty with time perception, and could easily be incorporated into individual education or behavior management plans.

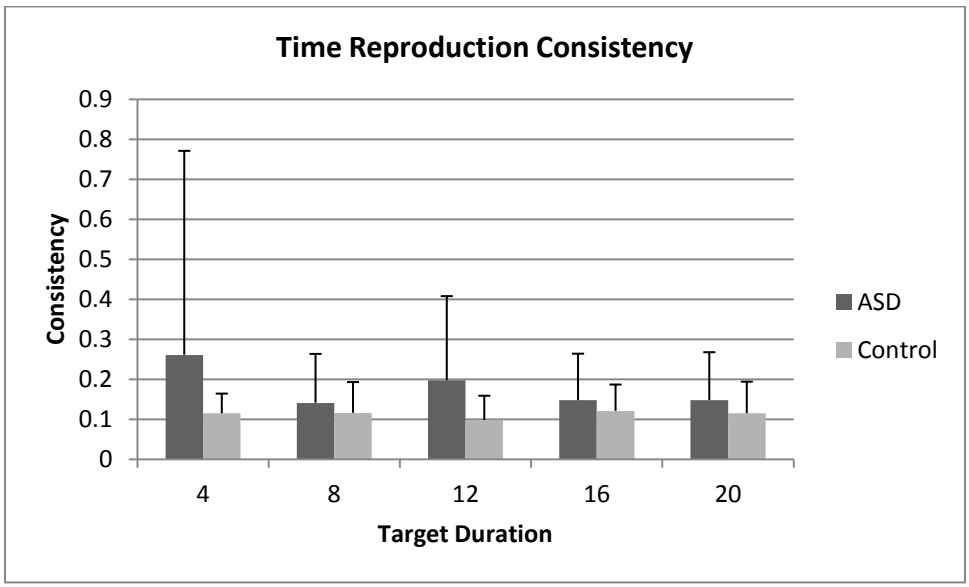
Table 1. Age, Sex, and IQ

Group	N	Age[1]	Sex (m:f)	IQ[2]
Control	25	13.41(2.32)	22:3	106.96(11.46)
Autistic Disorder	27	12.68(2.85)	23:4	101.31(11.24)

1. *Age in years, Mean (StDev)*
2. *WISC-IV Full Scale Intelligence Quotient, Mean(StDev)*

Figure 1. Time reproduction accuracy (average coefficient of accuracy) and consistency (standard deviation of the coefficient of accuracy) for the five target durations (4, 8, 12, 16, and 20) by group (ASD and control). For accuracy, values of 1 represent perfect accuracy and anything less than 1 is an under-estimation of the target duration. For consistency, lower values indicate better consistency and higher values indicate more variability in temporal reproductions.





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Chapter Three

Variability in temporal reproductions associated with chromosome 22q11.2 deletion syndrome

Abstract

Objective: Disturbances of time reproduction are associated with a range of neuropsychiatric conditions, including both attention-deficit/hyperactivity disorder (ADHD) and autism; however, much less is known timing abilities in 22q11.2 deletion syndrome (22q11DS). Although 22q11DS is associated with greatly elevated rates of ADHD and autism spectrum disorders in childhood, it is not yet known whether temporal processing deficits in 22q11DS are related to variability in the clinical phenotype. The objective of the present study was to: 1) characterize time reproduction abilities 22q11DS; and 2) assess the contribution of developmental factors, attention-related symptomotology and autistic traits to time reproduction performance in 22q11DS patients.

Method: Thirty-three individuals (ages 6-18) with a confirmed 22q11.2 deletion and 28 typically developing controls completed a time reproduction (TR) task and measures of cognitive function. Parent-reported ADHD symptoms and a measure of reciprocal social behavior (Social Responsiveness Scale; SRS) were also obtained.

Results: Repeated measures mixed effects regression analysis with diagnostic group, age, IQ and interval duration revealed a significant main effect only of interval duration on TR accuracy (longer interval durations were under-estimated), but no main effect of group, indicating that 22q11DS patients did not differ from controls on TR accuracy. However, there were significant main effects of diagnosis and age, as well as interval duration, on TR consistency. Younger children overall and individuals with 22q11DS were less consistent. Within the 22q11DS group, we used repeated measures regression analysis to predict response consistency and accuracy as a function of ADHD symptoms, SRS score, age, IQ, and interval duration. There was a significant

main effect of interval duration on both accuracy and consistency, and a significant main effect of age on consistency. Contrary to our predictions, task performance was not associated with clinical symptoms in 22q11DS, after accounting for the effects of interval duration and age. **Conclusions:** Variability in time reproduction performance is associated with younger age and 22q11DS diagnosis. These results suggest temporal processing deficits may be more generally related to frontal-striatal development and genetic influences on neurotransmitters in the prefrontal cortex rather than specific dimensions of psychopathology.

The 22q11.2 deletion syndrome (also known as velo-cardio-facial or DiGeorge syndrome) is the result of a hemizygous 1.5 to 3 megabase microdeletion at band 11.2 on the long (q) arm of chromosome 22 (Shprintzen, 2008) and is one of the most common genetic syndromes, with prevalence estimates range from 1:2,000 to 1:7,000 (Shprintzen, 2008). Although 22q11.2 deletion syndrome (22q11DS) is defined by a specific and known genetic anomaly, clinical presentation is highly variable. Over 180 clinical features have been associated with the deletion (Robin & Shprintzen, 2005). These include physical features, such as cleft palate, velopharyngeal insufficiency, hypernasality and cardiac defects, as well as endocrinological (e.g., hypocalcaemia) and neurological problems (seizures, mild developmental delay). Global estimates of intellectual functioning typically range from mild intellectual disability to low average, with a mean full-scale intelligence quotient of about 74 (see Antshel, Fremont, & Kates, 2008 for review). Additional clinical features include impaired visual attention, sensorimotor ability, and executive function (Sobin, Kiley-Brabeck, Daniels, Khuri, Taylor, Blundell, Anyane-Yeboa, & Karayiorgou, 2005).

In addition to the phenotypic characteristics outlined above, high rates of psychiatric disorders have been documented in 22q11DS, including psychosis, mood disorders, attention deficit/hyperactivity disorder (ADHD), and autism. ADHD is estimated to occur in 40% of individuals with 22q11DS (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2005). Estimates of autism spectrum disorder (ASD) co-morbidity range from 14% (Fine, Weissman, Gerdes, Pinto-Martin, Zackai, McDonald-McGinn, & Emanuel, 2005) to 50% (Antshel, Aneja, Strunge, Peebles, Fremont, Stallone, Abdulsabur, Higgins, Shprintzen, & Kates, 2007; Vorstman, Morcus, Duijff, Klaassen, Heineman-de Boer, Beemer, Swaab, Kahn, & van Engeland, 2006). There is also evidence that social dysfunction may characterize the broader phenotype in 22q11DS,

irrespective of ASD diagnosis (Kiley-Brabeck & Sobin, 2006). A dimensional approach to the quantification of social function and ADHD- symptomotology in 22q11DS has several advantages over the purely categorical approach. For example, dimensional assessment can better characterize the spectrum of phenotypic variability and its relationship to continuously distributed biological characteristics (e.g., brain morphology). It may also contribute to our understanding of divergent and overlapping clinical manifestations of psychopathology; in other words, a dimensional approach may help clarify which traits are present in all children with the deletion and why some children go on to develop ADHD, while others meet diagnostic criteria for ASD.

A dimensional approach to psychopathology is also complementary to the concept of intermediate phenotypes, or "endophenotypes." Endophenotypes are elemental characteristics or traits that vary along continua in the general population and are correlated with clinical manifestations of psychopathology (Almasy & Blangero, 2001). In some cases, endophenotypes are also "trans-diagnostic" in the sense that they transcend disorder-specific nosology and may operate as risk factors for multiple clinical syndromes (Nolen-Hoeksema & Watkins, 2011). A candidate endophenotype that may be of relevance to 22q11DS is temporal processing (e.g., time perception). Temporal processing is the basic human ability to perceive, estimate, and represent the passage of time. It occurs along a timescale ranging from microseconds (sound localization) to circadian rhythms (sleep/wake cycle) and is often classified according to the magnitude of the interval or duration to be processed. Specifically, researchers have proposed a distinction between temporal processing of events that are less than 2 seconds and those that exceed 2 or 3 seconds (Ivry & Spencer, 2004; Lewis & Miall, 2003a, 2003b; Szelag, Kowalska, Rymarczyk, & Poppel, 2002). This distinction is supported by differential recruitment of cognitive processes

(e.g., the role of memory in maintaining longer intervals 'online') and evidence from neuroimaging studies indicating that the cerebellum is critical for timing in the sub-second range but not for longer intervals (Lewis & Miall, 2003a; Mauk & Buonomano, 2004; Meck & Malapani, 2004). The striatum and frontal cortex are also key regions in the network involved in second-range timing (Hinton & Meck, 2004; Meck & Benson, 2002), although task variability in modality (visual vs. auditory) and experimental design (e.g., production, discrimination, reproduction) complicate interpretations of their relative contribution as a function of temporal magnitude (Meck & Malapani, 2004).

Deficits in temporal processing are well-documented in ADHD (Toplak, Dockstader, & Tannock, 2006) and are also observed across a range of other psychiatric and neurologic disorders, including autism, schizophrenia, and Parkinson's disease (Allman & Meck, 2011); however, little is known about temporal processing in 22q11DS. To our knowledge, there is only one prior published study of temporal processing in children with 22q11DS. This study utilized both a duration discrimination and a time reproduction task to assess millisecond-range temporal processing (Debbané, Glaser, Gex-Fabry, & Eliez, 2005). For the finger tapping task (time reproduction), individuals with 22q11DS evidenced decreased accuracy (tending toward underestimation) and greater variability when reproducing the target cadence. A limitation of the finger tapping method to assess time reproduction is the potentially confounding effect of motor dexterity, which is often affected in children with 22q11.2 deletion syndrome (Van Aken, Caeyenberghs, Smits-Engelsman, & Swillen, 2009). An alternative to the finger tapping method is the time reproduction task originally used by Barkley et al (1997), which requires a single button press to reproduce the interval, thereby making fewer demands on motor coordination. In addition to being well-validated in children and adults with ADHD, this task is more suitable for

measuring second-range time reproduction, which has been associated with frontal-striatal circuitry (Jech, Dusek, Wackermann, & Vymazal, 2005).

Temporal processing is also influenced by developmental factors. Although children as young as ten months of age are able to discriminate temporal intervals of varying length in the second-range (Brannon, Suanda, & Libertus, 2007), there is evidence that the precision of temporal estimates (i.e., repeatability or response consistency) follows a more protracted developmental trajectory (Chelonis, Flake, Baldwin, Blake, & Paule, 2004). For example, in large, ethnically diverse sample of children between the ages of 5 and 13, the precision of temporal reproductions increased as a function of age. Age-related changes in temporal processing from childhood to adolescence may also reflect differential recruitment of frontal-striatal-parietal circuitry (Smith, Giampietro, Brammer, Halari, Simmons, & Rubia, 2011), underscoring the importance of considering developmental effects on the accuracy and consistency of temporal reproductions. Individuals in our study ranged from 6 to 18, allowing us to model the effects of age from early childhood through adolescence.

Temporal processing deficits co-occur with ADHD (Toplak et al., 2006) and possibly also autism (Szelag, Kowalska, Galkowski, & Poppel, 2004), although findings have been mixed (e.g., see Wallace & Happe, 2008). As mentioned previously, 22q11DS is associated with an increased risk for both ADHD and autism spectrum disorder (ASD); thus, it provides a theoretical model for the study of how variability in temporal processing may be related to inattentiveness, hyperactivity, and social impairment. The purpose of this study was to: (1) characterize time reproduction in children and adolescents with 22q11DS relative to a typically developing comparison group and (2) assess the impact of co-morbid ADHD and autism traits on time reproduction accuracy and consistency within the 22q11DS group. We hypothesized that

the 22q11DS group would be less accurate and more variable in their temporal reproductions than the age- and sex- matched control group. Based on the established relationship between time reproduction and ADHD (see Toplak et al., 2006 for review), we expected that ADHD symptoms would be associated with reduced time reproduction accuracy and consistency. Finally, based on temporal processing research in typically developing children, we hypothesized that age would have a significant effect on the consistency of temporal reproductions in the overall sample, and that this effect would be stronger for individuals with 22q11DS.

Methods

Participants

The sample included 33 children and adolescents with molecularly confirmed deletions on chromosome 22 at band q11.2 (51% female) and 28 of their typically developing peers comparable for age and sex (50% female). All participants were between the ages of 6 and 18. Demographic data are listed in Table 1.

Procedures

Participants were recruited through distribution of fliers to research sites and genetic clinics as well as by word-of-mouth. Interested families contacted the research coordinator at the University of California, Los Angeles (UCLA) and underwent an initial phone screening to determine eligibility. Because 22q11DS is relatively rare, many of the families came to UCLA from out-of-state to participate. On the day of the visit, the child underwent cognitive testing, magnetic resonance imaging (MRI), a blood draw, and the Autism Diagnostic Observation Schedule (ADOS). The parent completed the Autism Diagnostic Interview – Revised (ADI-R), the Diagnostic Interview Schedule for Children (DISC), and a packet of questionnaires. An advanced graduate student in the clinical psychology program conducted the cognitive testing.

The DISC was administered by trained research assistants. Autism diagnostic measures were administered by trained staff at the UCLA Autism Evaluation Clinic and the final diagnosis was based on results of the ADI-R, ADOS, and clinical observation by an experienced clinician. All families received monetary compensation in the form of a check mailed to them after completion of the study as well as a summary report that included the results of cognitive testing and diagnostic impressions.

Parent-Report Measures

The *National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children, 4th edition* (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The DISC-IV is a fully structured diagnostic parent interview of child psychopathology. Multiple modules were administered, but for this analysis we focused only on ADHD. Specifically, we used the total number of inattention (range 0-9) and hyperactivity symptoms (range 0-9). This approach is supported by a meta-analysis of 546 studies showing that the DSM-IV symptom dimensions (i.e., inattention and hyperactivity/impulsivity) have better concurrent, predictive, and discriminant validity than nominal subtypes (Willcutt, Nigg, Pennington, Solanto, Rohde, Tannock, Loo, Carlson, McBurnett, & Lahey, 2012).

The *Social Responsiveness Scale* (Constantino & Gruber) is a 65-item parent-report measure designed to assess impairments in reciprocal social behavior. The total score captures observed social behavior in the domains of receptive, cognitive, expressive, and motivational aspects of social behavior, as well as autistic preoccupations. The SRS has good psychometric properties (Constantino, Davis, Todd, Schindler, Gross, Brophy, Metzger, Shoushtari, Splinter, & Reich, 2003; Constantino, Przybeck, Friesen, & Todd, 2000) and has proven efficacious as a measure of continuously distributed autistic traits in the general population (Constantino &

Todd, 2003). All raw scores on the SRS were converted to T-scores using the age- and sex-based normative data (Constantino & Gruber, 2005).

Neuropsychological Measures

The two-subtest (Vocabulary, Matrix Reasoning) version of the *Wechsler Abbreviated Scales of Intelligence* (Wechsler, 1999) was used to provide an estimate of global cognitive function. The WASI is nationally standardized and has good psychometric properties. The two-subtest WASI has an average reliability coefficient of 0.96 and test-retest reliability of 0.88. The scale yields a standardized estimate of intelligence, the Full Scale Intelligence Quotient (FSIQ), which has a mean of 100 and a standard deviation of 15.

Time Reproduction task (Barkley, 1998). This is a previously validated computerized task requiring estimation of a temporal duration and the execution of a motor response (i.e., the "reproduction") (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001). The task displays two light-bulbs simultaneously on the computer screen. The light-bulb on the left is turned on for an interval of 4, 8, 12, 16 or 20 seconds. When it goes off, the participant is asked to hold the space bar down to light up the bulb on the right for the same amount of time (i.e., to reproduce the interval). Participants practiced prior to the task to enhance comprehension. Each of the 5 temporal durations was repeated 4 times in random order, resulting in a total of 20 trials. No performance-based feedback was provided; however, given that motivational deficits associated with ADHD may influence performance (McInerney & Kerns, 2003), verbal praise was given to incentivize task engagement. Children also earned stickers for positive effort unrelated to task performance.

Data Analysis

The coefficient of accuracy (CoA) was used as the primary outcome measure of time reproduction performance. The CoA is calculated by dividing the subject's estimate of the temporal interval by the actual interval presented, yielding a percentage measure of error across the different durations. A score of 1.0 represents perfect accuracy whereas scores lower and higher than 1.0 represent under- and over-estimates, respectively. The CoA, which is also sometimes referred to as the duration judgment ratio, is a common outcome measures in studies of time reproduction (e.g., Hurks & Hendriksen, 2011; Kerns et al., 2001; Mullins et al., 2005; Plummer & Humphrey, 2008). Response *accuracy* was measured using the average CoA by averaging across the four repetitions of each trial type (4, 8, 12, 16, and 20 second durations). Response *consistency* ("variability") was measured by calculating the standard deviation of the four repetitions for each of the time durations. Variability has been less frequently examined than accuracy, with most studies to dating have used the average of either the coefficient of accuracy or the absolute discrepancy; however, there is evidence to suggest that the standard deviation of the coefficient of accuracy, as a measure of intra-individual variability, is an important consideration in time reproduction studies (Plummer & Humphrey, 2008). The independent variables in our study were age (range 6-18), FSIQ, sex, interval duration (4, 8, 12, 16, or 20 seconds), autistic traits (Social Responsiveness Scale Total Score), and DSM-IV inattentive and hyperactive symptoms.

We constructed repeated measures linear mixed effects models to predict (1) response accuracy (average CoA) and (2) response consistency (standard deviation of CoA). The explanatory factors were modeled as fixed effects with a random intercept for each subject, allowing for individual variation in time reproduction capabilities. There were no *a priori* hypotheses about the pattern of correlations (or covariances) among repeated measures, so an

unstructured covariance structure was specified. An alpha level of 0.05 was used for all statistical tests.

Results

Outliers and Group Differences

Initial examination of the data revealed significant outliers that biased mean estimates of performance. Taking a cautious approach, we only excluded outliers that were believed to reflect participant error (e.g., participant's finger slipped off the space bar). These outliers were defined as subject duration estimates of less than 0.15 seconds and constituted less than 1% of the total number of observations. Treatment of outliers in the data has not been consistently reported on in the time reproduction literature; however, our approach is consistent with methods used by Marx et al. (2010) where 1.75 % of the data points were deemed to reflect participant error.

Mean age, FSIQ, and sex distribution are listed in Table 1. As expected, the groups differed in overall intellectual functioning, $t(59)=8.45$, $p<.0001$; therefore, FSIQ was used as a covariate in all of the analyses. There was also a statistically significant between-group difference overall on the social responsiveness scale (SRS), $t(59)=4.51$, $p<0.0001$, with the greatest level of impairment for the 22q11DS group in the social behavior sub-domains of cognition (M=68, SD=14.17) and autistic mannerisms (M=67.76, SD=15.05). The hyperactivity symptom dimension, as measured by the C-DISC, was not well represented in our sample of children with 22q11DS (M=1.68, SD=2.4); therefore, we elected to treat ADHD symptoms as a single dimension (range 0-18). This approach is supported by confirmatory factor analytic studies supporting a unitary construct of ADHD (e.g., Toplak, Sorge, Flora, Chen, Banaschewski, Buitelaar, Ebstein, Eisenberg, Franke, Gill, Miranda, Oades, Roeyers, Rothenberger, Sergeant, Sonuga-Barke, Steinhausen, Thompson, Tannock, Asherson, &

Faraone). The 22q11DS group had significantly higher parent-ratings of total ADHD symptoms than the control group, $t(59)=5.87$, $p<.0001$. Means and standard deviations for the SRS total score and DSM-IV inattentiveness and hyperactivity symptom counts are listed in Table 1.

Between-Group Analyses

Repeated measures linear mixed effect models were run to predict accuracy of temporal reproductions, as a function of diagnosis (22q11DS versus control) and interval duration , adjusting for the effects of global intellectual functioning (IQ) and demographic variables (age and sex). Sex did not have a significant effect on time reproduction and was therefore excluded from further analysis. The final model included interval duration, age, IQ, and the interaction between age and diagnosis. The interaction between diagnosis and age, $F(1,240)=2.71$, $p=0.101$, was not a significant predictor of time reproduction accuracy. There was a significant main effect of interval duration, $F(4,240)=9.27$, $p<.0001$. The main effects of diagnosis, $F(1,240)=2.71$, $p=0.1008$, IQ, $F(1,240)=2.28$, $p=0.1320$, age, $F(1,240)=1.72$, $p=0.1912$ on response accuracy were not significant.

The second set of analyses focused on response consistency. Repeated measures regression analysis was used to predict the consistency of temporal reproductions (the standard deviation of the CoA) from diagnosis, interval duration, age, sex, IQ, and the interaction between diagnosis and age. Sex was not a significant predictor and was therefore excluded from the model. There was a significant interaction effect for diagnosis and age, $F(1,240)=2.40$, $p=0.1229$, on response consistency. There were significant main effects of diagnosis, $F(1,240)=4.25$, $p=0.0403$, interval duration, $F(4,240)=3.64$, $p=0.0067$, and age, $F(1,240)=22.35$, $p<.0001$ on time reproduction consistency. The main effect of IQ, $F(1,240)=0.63$, $p=0.4275$, on response consistency was not significant.

22q11DS Within-Group Analyses

To assess the relative contributions of ADHD and autism symptomotology to time reproduction accuracy *within* the 22q11DS group, repeated measures regression analyses were run with the independent variables interval duration, ADHD total symptoms (inattentiveness and hyperactivity), and SRS Total Score, adjusting for the effects of IQ and age. The rationale for the within-group analysis was to focus on clinical symptoms in 22q11DS that might impact response accuracy, but for which there would be insufficient variability in the control group. There was a significant main effect of interval duration, $F(4,127)=5.47$, $p=0.0004$. The main effect of age approached statistical significance, $F(1,127)=2.79$, $p=0.0971$. Neither total ADHD symptoms, $F(1,127)=1.30$, $p=0.2560$, nor SRS Total Score, $F(1,127)=0.46$, $p=0.5006$, nor IQ, $F(1,127)=0.78$, $p=0.3802$ was associated with time reproduction accuracy in children with 22q11DS

To assess the effects of co-morbid psychopathology on response consistency, a follow-up repeated measures regression analysis was run within the 22q11DS group. Predictors included interval duration, total ADHD symptoms, social responsiveness, IQ, and age. There were significant main effects of interval duration, $F(4,127)=3.00$, $p=0.0209$, and age, $F(1,127)=16.16$, $p<.0001$ on response consistency. However, ADHD symptoms, $F(1,127)=0.37$, $p=0.5452$, social responsiveness, $F(1,127)=1.82$, $p=0.1794$, and IQ $F(1,127)=1.06$, $p=0.3051$, were not significant predictors of response consistency.

Discussion

The goal of this study was to evaluate temporal processing, and its association with dimensions of psychopathology in children and adolescents with 22q11DS using a previously validated time reproduction task (Barkley, 1997, 1998). Results confirmed the hypothesis that

individuals with 22q11DS are more variable (less consistent) in their temporal reproductions than typically developing individuals. Younger age and longer interval durations were also associated with greater variability, which is consistent with prior research in typically developing children (Chelonis et al., 2004). However, contrary to expectations, response accuracy did not differ between groups. The only significant predictor of time reproduction accuracy was interval duration – as the length of the target duration increased, accuracy decreased, especially for the 12, 16, and 20 second trials. More specifically, the 12, 16, and 20 second durations were under-estimated on average.

This study is the first to attempt to relate time reproduction accuracy and consistency to dimensional assessment of psychopathology (i.e., ADHD symptoms and autism traits) in 22q11DS patients. We hypothesized that more severe ADHD symptomatology would be associated with lower accuracy and increased variability in temporal reproductions; however, this hypothesis was not confirmed. Within the 22q11DS group, neither ADHD symptomotology nor autism traits (as measured by the social responsiveness scale) had any effect on time reproduction performance. The only significant within-group predictor of response accuracy and consistency was interval duration – i.e., accuracy and consistency both decreased in response to increasing interval durations. This is surprising in light of abundant evidence connecting ADHD to deficits in time reproduction performance (e.g., see Toplak et al., 2006 for review). There are several possible explanations for our failure to find an effect of ADHD symptomotology. For one thing, our sample was more representative of the predominantly inattentive subtype, and hyperactivity/impulsivity symptoms were very low overall (see Table 1). In the ADHD literature, deficits in time reproduction have been reported most frequently for the combined type (e.g., Kerns et al., 2001; Valko, Schneider, Doehnert, Muller, Brandeis, Steinhausen, & Drechsler,

2010). Few studies have directly compared subtypes and the results have been mixed, with one study reporting more variable responding in the combined relative to the inattentive type (Mullins et al., 2005) and a second study showing no difference between the combined and inattentive subtypes (Bauermeister, Barkley, Martinez, Cumba, Ramirez, Reina, Matos, & Salas, 2005). Another possible interpretation of our findings is that temporal processing deficits are a feature of 22q11DS more generally, rather than a manifestation of co-morbid psychopathology. In other words, time reproduction deficits may not be unique to ADHD, or even to ADHD symptomotology more generally; rather, impairment in temporal processing may simply be a clinical correlate of aberrant neurodevelopment that co-occurs with, but is not causally related to, the clinical syndrome. Future research may be able to answer this question by investigating the relationship between neurobehavioral function (e.g., temporal processing) and genetic and neurobiological variability in different neurodevelopmental syndromes.

Converging evidence from studies of human interval timing in the supra-seconds range (i.e., durations spanning several seconds) implicates a core neurofunctional network involving the dorsolateral prefrontal cortex, striatum (caudate and putamen), thalamus (Hinton & Meck, 2004; Meck, Penney, & Pouthas, 2008), and possibly also the inferior parietal lobe (Smith et al., 2011). Neuroanatomical findings in 22q11DS suggest that frontal-striatal systems may be one of the sites of aberrant development: in addition to an overall reduction in brain volume (Campbell, Daly, Toal, Stevens, Azuma, Catani, Ng, van Amelsvoort, Chitnis, Cutter, Murphy, & Murphy, 2006; Kates, Burnette, Bessette, Folley, Strunge, Jabs, & Pearlson, 2004), there are reports of caudate asymmetry, consisting of a relatively larger right caudate nucleus (Sugama, Bingham, Wang, Moss, Kobayashi, & Eto, 2000) as well as reversed asymmetry (right greater than left) for the head of the caudate nucleus (Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2002) and bilateral

volumetric enlargement of the head of the caudate in individuals with 22q11DS relative to controls . Although there are not yet any functional imaging studies of temporal processing in 22q11DS, there is preliminary evidence for a relationship between temporal processing and caudate volume (Gabriel Mounir, Debbane, Schaer, Glaser, & Eliez). Following up on a prior study of temporal processing (Debbané et al., 2005), Gabriel Mounir and colleagues (2011) found between-group difference in caudate volume, with increased size in the 22q11.2 group relative to a typically developing control group. Interestingly, caudate volume was related to time perception in the control group but not the 22q11.2 group (Gabriel Mounir et al., 2011). It will be interesting to see whether future studies of timing in the second-range in 22q11DS are associated with neuroanatomic variability. Investigation of white matter connectivity via diffusion tensor imaging is another promising avenue of research for studies of frontal-striatal circuitry in 22q11DS and its relationship to time perception.

The neuropharmacology of temporal processing is also relevant to 22q11DS. Dopamine is the primary neurotransmitter used in connections within the basal ganglia and in projections from the basal ganglia to cortical regions (Bjorklund & Dunnett, 2007). For this reason, individual differences in dopamine function – as a result of genetic variation in dopamine-regulating genes, dopaminergic neuron loss (e.g., in Parkinson's disease), or pharmacological intervention (e.g., dopamine agonists such levodopa) – would be expected to influence activity in the mesostriatal and mesocortical pathways. These differences would also be putatively evident in 'downstream' effects, including cognitive and behavioral functioning. For the most part, what is known about the effect of disrupted dopaminergic signaling on temporal processing complements what is known from imaging studies about the involvement of frontal-striatal

systems (Ivry & Spencer, 2004; Jones, Malone, Dirnberger, Edwards, & Jahanshahi, 2008; Meck, 1996).

Of the many genes responsible for dopamine regulation and signaling in the frontal-striatal system, the catechol-O-methyltransferase (COMT) gene, located on chromosome 22q11 (within the deleted region in 22q DS), has emerged as an important candidate in the search for behavioral and neurophysiological phenotypes. The COMT enzyme is responsible for degradation of cortical dopamine, primarily in prefrontal regions, and specific allelic variations are associated with relatively more or less dopamine available in the synapse (Chen, Lipska, Halim, Ma, Matsumoto, Melhem, Kolachana, Hyde, Herman, Apud, Egan, Kleinman, & Weinberger, 2004). Allelic variation (i.e. the substitution of valine by methionine in the peptide sequence) in COMT has been associated with differences in time estimation performance (Reuter, Peters, Schroeter, Koebke, Lenardon, Bloch, & Hennig, 2005). Specifically, there is evidence that the Val allele is associated with a faster internal pacing mechanism and "speeded up" sense of time (Reuter et al., 2005). COMT Val 158 Met genotype also appears to be related to functions commonly associated with the prefrontal cortex (Diaz-Asper, Weinberger, & Goldberg, 2006). It is hypothesized that the relationship between prefrontal dopamine and cognitive performance may best be characterized by an inverted U-shape (Goldman-Rakic, Muly, & Williams, 2000); because patients with 22q11DS are missing 1 copy of this gene, they are likely shifted far to the right of this inverted U-curve, indicating disrupted dopaminergic neurotransmission. One theory that is pertinent to our findings suggests that COMT polymorphisms may cause a "prefrontal phenotype" characterized by either higher or lower than average dopamine levels, which disrupts temporal processing and leads to increased inter-trial variability and impaired time estimation (Castellanos & Tannock, 2002). Applied to this study,

the implication is that COMT haploinsufficiency, and perhaps allelic variation in the intact arm of chromosome 22, are contributing to response variability.

Given the prevalence of 22q11DS (~1:4000), our sample size was relatively small. This was a methodological limitation for the within-group analysis of psychopathological dimensions (e.g., social responsiveness, ADHD symptomotology). Data collection is still ongoing; replication of these findings when a larger sample is accrued, and/or at other sites would strengthen the implication that temporal processing deficits are not solely attributable to co-morbid psychopathology, but rather are broadly characteristic of the neurogenetic syndrome. This interpretation of our results would be in keeping with the "spatiotemporal hypergranularity" hypothesis (Simon, 2008), which is based on evidence that children with 22q11DS require a larger difference between temporal durations (Debbané et al., 2005) or spatial locations (Simon, Bearden, Mc-Ginn, & Zackai, 2005) in order to appreciate that they are distinct entities. Although we assessed time reproduction rather than temporal discrimination, the increased variability observed in our study suggests that children with 22q11DS do have trouble consistently providing an accurate reproduction. Finally, an additional limitation in this study was the use of a typically developing control group. Future research could address this limitation by comparing 22q11DS with other diagnostic groups, such as ADHD, autism, or another genetic syndrome that is associated with intellectual disability.

Our findings suggest that temporal processing deficits are not unique to "idiopathic" ADHD or autism, and may be useful as a clinical measure of frontal-striatal function that, in concert with other executive functions (e.g., attention, working memory) may in some cases be predicative of higher levels of emergent psychopathology (e.g., autism or ADHD). Conceptualizing psychopathology as the emergence of symptom clusters within a system of

dynamically interacting processes is consistent with the trans-diagnostic network model proposed by Borsboom and colleagues (2011). Examining the strength of causal links between variables in the network that are moderated or mediated by other processes may help better characterize comorbidity patterns and individual differences (Borsboom et al., 2011). The identification of specific traits that tend to cluster together and confer risk for difficulties in other areas, independent of disorder-specific nosology, thus has the potential to clarify unique and shared pathways in the pathophysiology of neurodevelopmental disorders. In view of the fact that several different psychopathological traits occur at high rates in 22q11DS, it is a population that has proven useful as a model for the study of symptom constellations and will be an important asset in the development of new theories of psychopathology.

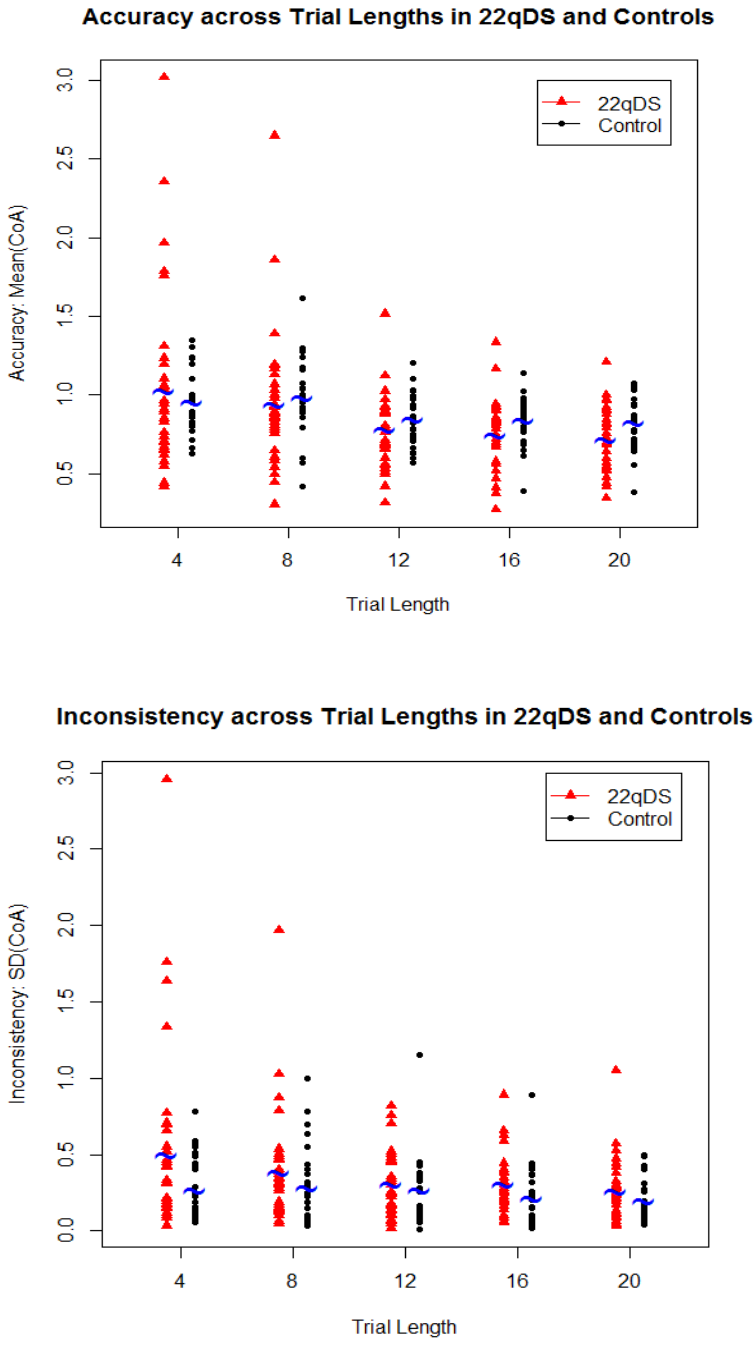
Table 1. Means and standard deviations for age, IQ, social responsiveness, and DSM-IV inattention and hyperactivity/impulsivity symptoms

Group	Sex	Age	IQ	SRS Total[1]	DSM-IV Inatt[2]	DSM-IV Hyper[3]	DSM-IV Total ADHD[4]
Control (n=28)	14 males	11.17 *(3.97)*	112.82* *(18.82)*	50.54* *(13.33)*	1.35 *(2.08)*	0.69 *(1.22)*	2.04* *(2.64)*
22q11DS (n=33)	17 males	11.95 *(3.34)*	77.30* *(13.97)*	66.97* *(14.86)*	4.84 *(3.08)*	1.68 *(2.40)*	6.52* *(4.34)*

**significant group difference, p<.05*

1. *Social Responsiveness Scale, Total T-Score, Mean(StDev)*
2. *Diagnostic Interview Scale for Children, DSM-IV Inattention Criteria for Attention Deficit Hyperactivity Disorder, Symptom Count (9 possible), Mean(StDev)*
3. *Diagnostic Interview Scale for Children, DSM-IV Hyperactivity/Impulsivity Criteria for Attention Deficit Hyperactivity Disorder, Symptom Count (9 possible), Mean(StDev)*
4. *DSM-IV Inattention and Hyperactivity/Impulsivity symptoms combined (18 possible)*

Figure 1. Time reproduction accuracy (average coefficient of accuracy) and consistency (standard deviation of the coefficient of accuracy) for the five target durations (4, 8, 12, 16, and 20) by group (22q and control). For accuracy, values of 1 represent perfect accuracy and anything less than 1 is an under-estimation of the target duration. For consistency, lower values indicate better consistency and higher values indicate more variability in temporal reproductions.



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